REMARKS/ARGUMENTS

Claims 1 to 12, 21 to 25, 31 to 37, and 39 to 43 are pending in the application. Claims 1, 22, and 39 have been amended herein. No new claim have been added, and no claims have been canceled, herein. Because the amendments remove issues for appeal, Applicants respectfully request entry thereof. MPEP § 714.13.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Preliminarily, Applicants note that claim 1 has been amended to recite, *inter alia*, a compound comprising uricase covalently bonded via a linking group to polyethylene glycol of a total weight average molecular weight of about 12,000 to about 30,000. Claim 22 has been amended to recite, *inter alia*, a method of enhancing the circulating half life of uricase comprising modifying the uricase by covalently bonding the uricase via a linking group to polyethylene glycol of a total weight average molecular weight of about 12,000 to about 30,000. Claim 39 has been amended to recite, *inter alia,* a compound comprising uricase coupled to polyethylene glycol of a total weight average molecular weight of about 12,000 to about 30,000. Support for the amendments is found in the specification as filed at, for example, page 10, lines 13 to 18. No new matter has been added.

Alleged Lack of Enablement

Claims 1 to 47[1] have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action acknowledges that the specification is enabling for polyethylene glycol of a weight average molecular weight of 5,000 or 20,000 bound to

[1] Applicants note that claims 1 to 12, 21 to 25, 31 to 37, and 39 to 43 are pending in the application.

uricase at unknown residues, but asserts that the specification fails to teach the effect that binding uricase to polyethylene glycol of molecular weights of 15,000 to 30,000 would have on the circulating half-life and biological activity of the enzyme. Applicants respectfully traverse the rejection because Applicants have demonstrated that uricase covalently bound to polyethylene glycol of weight average molecular weights of 12,000 to 40,000 retains approximately 75% of the biological activity of native uricase, and as the molecular weight of the polyethylene glycol bound to uricase increases from 5,000 to 30,000, the circulating half-life of the PEG-uricase increases from 8 to 84 hours.

As explained in the attached Declaration of Mike A. Clark, an inventor of the subject matter defined by the claims of the present application, Applicants have performed experiments in which purified *Candida utilis* uricase was covalently bound to polyethylene glycol of weight average molecular weights of 5,000; 12,000; 20,000; 30,000; or 40,000 via a succinimidyl succinate linking group. The PEG-uricase conjugates retained a substantial amount of enzymatic activity. More specifically, uricase-PEG 5,000; uricase-PEG 12,000; uricase-PEG 20,000; uricase-PEG 30,000; and uricase PEG 40,000 retained 55%, 73%, 75%, 74%, and 76% of the enzymatic activity of native uricase, respectively. In addition, as the molecular weight of the polyethylene glycol to which the uricase was bound increased, the circulating half-life of the pegylated uricase also increased. For example, uricase-PEG 5,000; uricase-PEG 12,000; uricase-PEG 20,000; uricase-PEG 30,000; and uricase PEG 40,000 had circulating half-lives of 8, 24, 72, 84, and 77 hours, respectively. Applicants have therefore demonstrated that purified *Candida utilis* uricase covalently bound to polyethylene glycol of weight average molecular weights of 12,000 to 40,000 retained approximately 75% of the biological activity of native uricase, and as the molecular weight of the polyethylene glycol

bound to uricase increased from 5,000 to 30,000, the circulating half-life of the PEG-uricase increased from 8 to 84 hours.

Applicants have therefore demonstrated the effect that binding uricase to polyethylene glycol of weight average molecular weights of 5,000 to 40,000 has on the biological activity and circulating half-life of the enzyme. Applicants, accordingly, respectfully request withdrawal of the rejection.

Alleged Obviousness

A. Claims 1 to 7, 9 to 12, 21 to 25, 31 to 37, and 39 to 43 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,460,683 (hereinafter "the Gloger patent") in view of either U.S. Patent No. 4,179,337 (hereinafter "the Davis patent") or Zapilsky, *et al.*, *Topics in Applied Chemistry*, 347-370 (1992) (hereinafter "the Zapilsky reference"). Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

Prior art references that serve as the basis of an obviousness rejection must be considered by the Patent Office in their entirety, *i.e.*, ***the references must be considered as a whole***, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)). "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *See Bausch & Lomb, Inc. v. Barnes-Hind, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986)(quoting *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965)).

The Office Action asserts that those of ordinary skill in the art would have been motivated to combine the teachings of the Gloger and Davis patents because the Davis patent allegedly teaches that conjugating proteins to polyethylene glycol reduces the antigenicity of the conjugates. When considered as a whole, however, the Davis patent fails to teach or suggest that conjugating straight or branched-chain polyethylene glycol to polypeptides decreases the antigenicity of the PEG-conjugated polypeptides. Accordingly, those of ordinary skill in the art would not have been motivated to combine the patent's teachings with those of the Gloger patent and would not have had a reasonable expectation of success for the combination. Moreover, even if those of ordinary skill in the art would have been motivated to combine the teachings of the Davis and Gloger patents, the combination fails to teach or suggest all the limitations of the present claims.

The Gloger patent teaches that uricase can be obtained from *Candida utilis* and *Aspergillus flavus*. The Davis patent fails to teach or suggest that coupling both linear and branched-chain polyethylene glycol to a polypeptide reduces the antigenicity of the conjugated polypeptide. The patent, in fact, teaches that branched polymers generate an immunogenic response when bound to a polypeptide:

> The polymers utilized for protection purposes in the procedures of the present invention possess a substantially linear ethereal or carbon carbon backbone. ***It has been found that utilizing branch chain polymers will give rise to substances which do generate an immunogenic response.***

Col. 2, lns. 43 to 48 (emphasis added). The patent, therefore, suggests that linear polyethylene glycol may reduce the antigenicity of a PEG-polypeptide conjugate, but also teaches that branched polyethylene glycol conjugated to a polypeptide would fail to reduce the antigenicity of the conjugate and would, in fact, generate an immunogenic response.

Accordingly, those of ordinary skill in the art would not have reasonably expected that ***straight or branched-chain*** polyethylene glycol could have been successfully conjugated to uricase to yield a conjugate that would have exhibited reduced antigenicity relative to native uricase. Those of ordinary skill in the art, therefore, would not have been motivated to conjugate uricase to straight or branched-chain polyethylene glycol, and, thus, would not have been motivated to combine the teachings of the Gloger and Davis patents. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have led those of ordinary skill in the art to combine the teachings of the Davis patent with those of the Gloger patent. In addition, the Office Action has failed to demonstrate that those of ordinary skill in the art would have had a reasonable expectation of success for the combination.

Moreover, assuming *arguendo* that those of ordinary skill in the art would have been motivated to combine the teachings of the Gloger and Davis patents, which Applicants do not concede, the combination fails to teach or suggest all the limitations of the present claims. The specification defines "polyethylene glycol" as "mixtures of condensation polymers of ethylene oxide and water, ***in a branched or straight chain***, represented by the general formula $H(OCH_2CH_2)_nOH$, wherein n is at least 4." See page 8, lines 29 to 31 of the specification as filed (emphasis added). The claims, therefore, recite uricase covalently bound to straight or branched-chain polyethylene glycol. As previously discussed, the Davis patent teaches that ***only linear*** polyethylene glycol reduces the antigenicity of PEG-polypeptide conjugates. A combination of the Gloger and Davis patents, therefore, fails to teach or suggest that straight ***or branched-chain*** polyethylene glycol would reduce the antigenicity of a PEG-uricase conjugate. Accordingly, the combination fails to teach or

suggest all the limitations of the present claims, and the Office Action has, therefore, failed to establish *prima facie* obviousness. Applicants accordingly, respectfully request withdrawal of the rejection.

With respect to the Zapilsky reference, when the reference is considered as a whole, it becomes apparent that the reference fails to teach or suggest that conjugating polyethylene glycol to a polypeptide necessarily decreases the antigenicity of the PEG-conjugated polypeptide. Furthermore, the reference fails to teach or suggest that conjugating polyethylene glycol to a polypeptide necessarily increases the circulating half-life of the conjugated polypeptide. Accordingly, those of ordinary skill in the art would not have been motivated to combine the reference's teachings with those of the Gloger patent and would not have had a reasonable expectation of success for the combination.

The Zapilsky reference fails to teach or suggest that coupling polyethylene glycol to a polypeptide necessarily reduces the antigenicity of the conjugate. The reference, in fact, teaches that when adenosine deaminase was conjugated to polyethylene glycol, "no reduction of the immunogenecity was reported." (See page 360). Furthermore, the reference also reports that conjugation of *E. coli* asparaginase to PEG 5000 showed a reduction in agnigenicity, while conjugation of the enzyme to PEG 750 and PEG 1900 "did not show a substantial change of the immunogenic properties." (See page 361). Finally, the reference states that PEG-conjugated gulonolactone oxidase "retained immunogenicity and reacted with preformed antibodies." (See page 362). When considered as a whole, the Zapilsky reference, therefore, teaches that conjugation of polyethylene glycol to polypeptides sometimes fails to reduce the antigenicity of the conjugates. Those of ordinary skill in the art, therefore, would not have reasonably expected that polyethylene glycol could have been

successfully conjugated to a polypeptide such as uricase, to yield a conjugate that would have necessarily exhibited reduced antigenicity relative to native uricase. Those of ordinary skill in the art, therefore, would not have been motivated to combine the teachings of the Gloger patent with those of the Zapilsky reference.

In addition, the Zapilsky reference fails to teach or suggest that coupling polyethylene glycol to a polypeptide necessarily increases the circulating half-life of the conjugate. The reference, in fact, teaches that when polyethylene glycol was conjugated gulonolactone oxidase "[t]he circulating half-life of the modified enzyme was not extended." (See page 362). When considered as a whole, the Zapilsky reference, therefore, teaches that conjugation of polyethylene glycol to polypeptides sometimes fails to increase the circulating half-life of the conjugates. Those of ordinary skill in the art, therefore, would not have reasonably expected that polyethylene glycol could have been successfully conjugated to uricase to yield a conjugate that would have necessarily exhibited an increased circulating half-life. Those of ordinary skill in the art, therefore, would not have been motivated to combine the teachings of the Gloger patent with those of the Zapilsky reference. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have led those of ordinary skill in the art to combine the teachings of the Zapilsky reference with those of the Gloger patent. In addition, the Office Action has failed to demonstrate that those of ordinary skill in the art would have had a reasonable expectation of success for the combination. Accordingly, the Office Action has failed to establish *prima facie* obviousness, and Applicants respectfully request withdrawal of the rejection.

B. Claims 1 to 5, 8 to 12, 21 to 25, 31 to 37, and 39 to 43 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chua, C., *et al.*, *Annals of Internal Medicine* 109:114-117 (1988) (hereinafter "the Chua reference") in view of either the Davis patent or the Zapilsky reference. Applicants respectfully traverse the rejection because the Office Action has failed to establish *prima facie* obviousness.

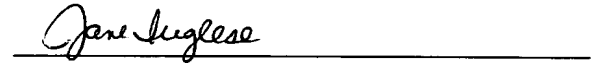
The Chua reference teaches that uricase can be obtained from *Arthrobacter protoformiae*. Applicants respectfully submit that, for the reasons stated above, upon review of either the Davis patent or the Zapilsky reference, those of ordinary skill in the art would not have been motivated to conjugate the uricase described in the Chua reference to polyethylene glycol and, accordingly, would not have been motivated to combine the teachings of the Chua reference with those of either the Davis patent or the Zapilsky chapter. Moreover, those of ordinary skill in the art would not have had a reasonable expectation of success for either combination. The Office Action, therefore, has failed to provide credible evidence of a motivation, teaching, or suggestion that would have led those of ordinary skill in the art to combine the teachings of either the Davis patent or the Zapilsky chapter with those of the Chua reference. In addition, the Office Action has failed to demonstrate that those of ordinary skill in the art would have had a reasonable expectation of success for either combination. Accordingly, the Office Action has failed to establish *prima facie* obviousness, and Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

Date: July 29, 2003



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